Cloudy with a chance of meatballs

or is it just precipitation.............
Current options from NHSBT

- UK Sourced (for adults)
  - Fresh frozen plasma
  - Cryoprecipitate (pooled)
  - Cryoprecipitate (singles)

- Non-UK sourced (for patients born after 1/1/1996)
  - Fresh frozen plasma Methylene Blue treated (paediatric)
  - Fresh frozen plasma Methylene Blue treated (neonatal)
  - Cryoprecipitate Methylene Blue treated (singles)
  - Cryoprecipitate Methylene Blue treated (pools)
Standard FFP (UK-sourced)

• Destined for general use in patients born before 1/1/1996

• Standard adult FFP (primarily WB derived, some from Apheresis)

• Single unit cryoprecipitate

• Pooled Cryoprecipitate

• Cryoprecipitate depleted plasma (now defunct)
Imported plasma

vCJD low risk plasma components

Rationale:
• Children born after the BSE ‘clean-up’ of the food chain in the 1990s deserved ‘clean’ blood components wherever possible.
• Decision applied to all patients born on or after 1\textsuperscript{st} January 1996
• They are our future blood donors...
Imported plasma

- Global assessment of a suitable source of plasma for importation into UK
- Performed by DH
- Based on variety of factors including indigenous cases of vCJD, BSE cases in cattle, ability to supply volume and ABO mix, suitable logistics etc.
- USA was agreed as primary target supplier
The successful US supplier

After 8 or 9 expressions of interest to supply, only one blood service in the US ultimately believed they could provide plasma to the very high specifications required by NHBST.
Importation from USA commenced in 2003

- Several test runs were performed to identify the most appropriate logistics

- Viral epidemiology was different from UK and Pathogen inactivation was implemented to counter any perceived increased risk of viral transmission. Methylene Blue treatment was initiated
Plasma supplied from 16 blood centres across the west and mid-west of the USA
Raw plasma provided by BSI and remanufactured by NHSBT

- Paediatric MB treated/removed FFP
- Neonatal MB treated/removed FFP
- Single unit MB treated/removed cryoprecipitate
- Pooled MB treated/removed cryoprecipitate
EU Directive

- Requires importing agencies to ensure that suppliers collect and manufacture in accordance with EU legislation
- US Blood Services must collect in line with FDA regulations
- NHSBT was recommended to seek a supplier from within the EU at next contract if possible
- Only 3 countries in EU met the DoH requirements
- Only 1 of these 3 (Austria) could also meet the supply requirements in terms of quantity and ABO mix
Austrian plasma now comes from two blood centres:
Austrian plasma

- Deliveries once – twice per month
- Approximately 850 units per shipment
- Transported below -25 °C
- Manchester and Colindale blood centres for Methylene Blue treatment, remanufacture and labelling
So what else is out there?
SDFFP from Octapharma
SDFFP

- Solvent-Detergent treated Fresh Frozen Plasma
- 200 mL product, frozen storage required
- Pooled product (approximately 1500 units in each pool)
- Enveloped viruses inactivated
- Non-enveloped viruses (e.g. HAV, HEV and Parvovirus) not inactivated but theoretically neutralised by insistence on a minimum level of antibody in the pool and by genomic testing of the plasma pool.
- Said to offer a low risk of TRALI
Theoretical options for Octaplas

- Octaplas (being superseded by Octaplas LG)
- Octaplas LG (prion reduced)
- Uniplas (universal) (?not yet available in UK)
- Uniplas Lyophilised (?not yet available in UK)
Liquid Plasma
Liquid plasma

- Plasma that has never been frozen or frozen and then thawed
- Kept liquid for a number of days at 4°C
  - Subsequently discarded or frozen and stored
- **Sweden** has routinely used this component for many years
  - Up to 7 days recommended
  - Up to 14 days allowed
  - Now considering PI to reduce risk of non-frozen storage

- May be useful in trauma situations as first line transfusion whilst awaiting FFP to be thawed

“Use in trauma situations for critically bleeding patients may improve speed of treatment, eliminating delays associated with thawing frozen plasma, and thereby improve patient care.” (Knutson et al 2011)
When speed and convenience is of the essence.....
Military drivers for alternatives to FFP

- FFP use is impractical in uncertain environments such as a battlefield.

- During military operations, refrigerated transportation and storage are logistical problems.

- Thawing of FFP takes a long time, with an important loss of plasma in austere environments.

For example, Mabry and colleagues reported that, during the Mogadishu urban battle, the available FFP was stored in bags that fractured one-third of the time upon thawing.

Daban et al 2010
Spray Drying

Background: Spray drying techniques are commonly utilized in the pharmaceutical, dairy and animal feed industries for processing liquids into powders but have not until recently been applied to human blood products.
Spray Dried Plasma

- Spray drying – Liquid solvent is forced through heated gas resulting in rapid dehydration on a sub-second timescale.
- Resulting powder has approximately 2.5% moisture content (long term storage).
- Various rehydration fluids e.g. Citrate/Phosphate Buffer, pH adjusted, 1.5% Glycine or just deionised water.
Resusix™ from Entegrion
Resusix™ - Spray Dried Solvent Detergent Treated™

• Research partially funded by various US military departments

• Derived from pools of human plasma, Resusix® is solvent detergent-treated and spray-dried to provide a safe, shelf-stable, readily available plasma

• Pooling different ABO groups reduces ABO antibody levels by neutralisation
Resusix™ claims

Provides benefits equivalent to FFP without:

- TRALI
- Viral transmission
- Cell fragments
- Variability

- Allergic reactions
- Lipids
- Other micro particles
- TRIM
Resusix™

Final presentation may be flexible:

• 1x - 14g powder/200mL fluid or 28g/400mL
• 3x – 14g powder/67mL fluid or 28g/133mL

• Reduces risk of volume overload
• Hyperoncotic and hyperosmotic
Resusix™

With an extended shelf life of more than two years at ambient temperature, the longer storage capacity breaks the cold chain restrictions of frozen blood plasma.

When Resusix® is commercially available (in the USA), the dehydrated plasma and reconstitution fluid will be packaged together for rapid combination when needed for immediate use.
SPRAY from Velico Medical

SPRAY: Single Donor Plasma Product For Room Temperature Storage

• Benefits of being a single donor product
• Single use disposable processing sets
• Relatively new entrant into the market
• Unclear on any patent issues (ref Resusix™)
• Velico looking for business partners to develop
Lyophilised plasma
Circa 1950’s

The life-saver. In the form of dried plasma, the blood donor’s gift is preserved so that it can be used months later on distant battlefields.
German Red Cross – West

Lyophilised plasma

Lyoplas N – may have originated as a collaboration between German Red Cross and Octapharma

Spin frozen and freez-dried human plasma was already introduced by Octapharma in 1992
Lyophilised Plasma LyoPlas N - w

• LyoPlas N – w is a freeze-dried plasma product derived from a single donation.
• Lyoplas N – w is used in the same indications as therapeutic frozen plasma.
• Plasma transformed into LyoPlas N – w undergoes an additional cell reduction step to render it virtually cell-free and highly compatible.
• LyoPlas N – w is available in all blood groups: O, A, B, AB.
• LyoPlas N - w may be stored at its place of use at temperatures between +2°C and +25°C
Some issues over reconstitution
Final liquid product a little cloudy
Some discussion ongoing as to whether this should be a blood component or a licensed pharmaceutical
French Military FDSP

Freeze Dried and Secured Plasma

• Each plasma unit is quarantined until subsequent donation has been tested

• Approximately 10 plasma units of mixed ABO groups are pooled

• ABO group selection is used to cause neutralisation of ABO antibodies in the pool

• Plasma is prepared as aliquots and lyophilised

• Pathogen inactivated
French Military FDSP

• Shelf stable at ambient temperature for 2 years
• Rehydrated with 200 ml water in 3 minutes for immediate use.
• Since 2010 such plasma has been photochemically treated

Claim...“FDSP contains all clotting factors and proteins. After more than 2 years storage at ambient temperature, the fibrinogen and clotting factor levels of FDSP are equivalent to FFP“
Developments in Universal Plasma

- Usual method is to supply AB FFP
- Alternatives are to pool a mix of ABO groups and use the soluble blood groups substances present to neutralise ABO antibodies
- New development work going on in at least two countries (US and UK) to produce a low cost ABO antibody removal filter for single donor plasma.
Thank You